REMARKS

Status of Claims

Claims 1-4, 7, 12-14, 20-22, 28-30, 36-38 and 44-46 are currently pending in the application. The Examiner has maintained her rejection of all of these claims except for claim 7 (i.e., claims 1-4, 12-14, 20-22, 28-30, 36-38 and 44-46) as lacking adequate enablement for any CAM molecule other than CAM B7.1. The Examiner has also maintained her rejection of all of these claims (i.e., claims 1-4, 7, 12-14, 20-22, 28-30, 36-38 and 44-46) as obvious in view of the combination of Futami et al. and Olsson et al.

As discussed below, Applicants respectfully observe that, with regard to the enablement rejection, the Examiner has not addressed the specific demonstrations already given by Applicants that CAMs other than CAM B7.1 are enabled as requiring only routine experimentation, rather than impermissible undue experimentation. This observation notwithstanding, solely to expedite prosecution and reduce issues on appeal Applicants have amended the claims, specifically claims 1-4, to remove any reference to CAMs other than CAM B7.1, thereby removing the enablement rejection. In light of the amendments to claims 1-4, claim 7 is now repetitive; therefore, Applicants have canceled claim 7.

With regard to the obviousness rejection, as discussed below, Applicants have shown that there is no motivation to combine the two references cited by the Examiner of Futami et al. and Olsson et al.; that there is no reasonable expectation of success even when these references are combined; and that, perhaps most significantly, even when combined these references emphatically do not teach every limitation of the claims, for example the DMXAA of all the claims. Therefore, on these bases the obviousness rejection must be withdrawn.

In light of the above, after the amendments to claims 1-4 and the cancellation of claim 7, claims 1-4, 12-14, 20-22, 28-30, 36-38 and 44-46 are now pending in the

application. Applicants note that no new subject matter has been added by way of any of the amendments to the claims.

Priority

Applicants thank the Examiner for entering the priority information provided by Applicants, specifically the claim to priority to New Zealand application NZ33629.

The Rejection of The Claims Under 35 U.S.C. § 112, First Paragraph As Lacking Adequate Enablement Must Be Withdrawn

The Examiner has maintained her rejection of 19 of the 20 outstanding claims, i.e., claims 1-4, 12-14, 20-22, 28-30, 36-38 and 44-46, as lacking enablement. Specifically, the Examiner continues to argue that there is enablement only for DMXAA in combination with the CAM B7.1 (i.e., the combination in claim 7), and that the practice of the invention with DMXAA and any of the other CAM molecules of the invention of B7.2, VCAM-1, MAdCAM-1, and ICAM-1 is not enabled because no guidance or actual experimental data was presented in the specification to show that these CAMs substitute for B7.1. Thus, the Examiner states,

> The specification does not provides [sic] direction/guidance or any test result that [the] combination of the [sic] CAM except [for the] B7.1 gene with DMXAA could result in a better treatment for the large tumor than any the [sic] reagent alone.

Office Action of 1/16/2007, page 4 at bottom, emphases added. In the absence of such data, the Examiner concludes,

> Because [of] the nature of the invention and unpredictable treatment result, one skilled in the art would be forced into under [sic] experimentation in order to practice the claimed invention [with the other CAMs B7.2, VCAM-1, MAdCAM-1, and ICAM-1].

Office Action of 1/16/2007, page 4 at bottom.

With regard to the second of the Examiner's arguments, i.e., that there are no experimental data on the use of CAMs other than B7.1, both Applicants and the Examiner are of course aware that such data is not necessary if sufficient guidance is provided in the specification. Thus, for example, prophetic experiments are completely acceptable forms of guidance, and actual experiments are not required. Thus Applicants will focus solely on the Examiner's first argument about the lack of guidance in the specification.

With regard to the first argument made by the Examiner that there is no direction/guidance in the specification for the routine (as opposed to undue) experimentation required to provide enablement of any CAM molecules other than B7.1, in fact there is an abundance of such guidance for routine experimentation, which Applicants respectfully note was already presented to the Examiner for her consideration in the Response filed by Applicants on 6/7/06.

Specifically, as Applicants stated at length in the Response of 11/22/06 (as well as in the Response of 6/7/06), experimentation is allowable as long as it is not undue. Thus as Applicants stated in the Response of 11/22/06, page 10, middle paragraph,

> With regard to this [enablement] rejection, Applicants note at the outset that the standard for determination of adequate enablement is not whether some experimentation is required, but rather whether "any person skilled in the art can make and use the invention without undue experimentation (Manual of Patent Examining Procedure (MPEP) § 2164.01, citing In re Wands, 858 F.2d at 737, 8USPQ2d at 1404 (Fed. Cir. 1988); emphasis added). Thus the question with regard to the present rejection is whether the experimentation required to practice the invention as disclosed in the claims is actually undue, or whether it is in fact merely routine, with routine experimentation proof that the claims are enabled.

Emphases in original. There is abundant guidance in the specification for the use of other CAMs than B7.1; e.g., as already stated to the Examiner in the Response of 6/7/06 (page 10, second paragraph), ¶ 40 of the specification describes the numbers and sources for numerous CAM molecules, including B7.1, ¶ 9 of the specification provides expression vectors for production of CAM proteins, etc.

Furthermore, CAM proteins themselves were well known in the art at the time; for example, the Examiner herself has cited Olsson et al. for the proposition that a variety of CAMs have been studied for their effects on cells (see also the discussion below of the Examiner's obviousness rejection).

Thus there is no reason whatsoever to find the substitution of other CAMs than B7.1 to be anything other than routine, and the enablement rejection of the claims must in fact be withdrawn on the basis of the above discussion.

Notwithstanding the above, solely in order to reduce the number of issues presented in this application, and more specifically in order to reduce the issues to be discussed on appeal, Applicants have amended the claims to remove any reference to any CAM except B7.1. These amendments have been made to expedite prosecution and for appeal purposes only; Applicants have not varied from their previous observation that the enablement rejection of other CAMs is inapposite, and should be withdrawn.

The Rejection of The Claims Under 35 U.S.C. § 103(a) As Obvious Must Be Withdrawn

The Examiner has also maintained her rejection of all 20 of the outstanding claims as obvious in light of the combination of Futami et al. and Olsson et al. Specifically, the Examiner 1) observes that Futami teaches a combination of IL-2 and analogs of XAA to treat cancer, and on this basis 2) argues that Futami

therefore teaches IL-2 plus the DMXAA of the invention by extrapolation to DMXAA from the analogs of XAA used in the Futami reference. The Examiner then 3) observes that Olsson shows that IL-2 production in cancer cells goes up when CAM B7.1 is administered, such that, the Examiner states,

> Olsson et al., teach Human IL-2 is induced by CD80 (B7.1) in cancer cells and T cells, which indicate [sic] that CD80 (B7.1)'s action on eradication of tumor is through induction of IL-2 and activation of T-cell by IL-2 for killing tumor cells. Therefore, replaced [sic] IL-2 with its stimulator B7.1 would result in same treatment effect and one of ordinary skill would be motivated to reached the claimed invention ...

Office Action of 1/16/07, page 6 in top third of page, emphasis added. That is, in the above quotation the Examiner 4) argues the results of Olsson suggest a general mechanism of tumor killing involving using B7.1 to induce IL-2 and activate T-cells (see above quote), so that 5) the Examiner then argues that the results of Olsson suggest replacing the IL-2 of Futami with a molecule that stimulates IL-2 production, B7.1, such that 6) the Examiner argues that the combination of Futami and Olsson suggests the use of B7.1 with DMXAA, thereby rendering obvious all of the present claims. For the Examiner's convenience, this sequence of the Examiner's logical steps 1-6 is summarized in tabular form below:

LOGIC STEP	FACT	EXAMINER'S ARGUMENT	FACT	EXAMINER'S ARGUMENT
1 Futami (Fact)	Teaches XAA analogs; **NOT** DMXAA; 1 of 3 analogs **DOESN'T WORK**.		Teaches IL-2	
2 Futami (Examiner's argument)		Examiner concludes that XAA analogs imply DMXAA	Teaches IL-2	
3 Olsson (Fact)			Teaches CAM B7.1 increases IL-2 (and a lot of other compounds)	
4 Olsson (Examiner's argument)				Examiner concludes that CAM B7.1 acts on tumors via IL-2 to induce IL-2 and activate T-cells

5 Olsson (Examiner's argument)				Examiner concludes that the skilled artisan would replace IL-2 with CAM B7.1.
6 Futami plus Olsson (Examiner's argument)		**DMXAA**		**CAM B7.1**

With regard to these arguments, first, as noted in step 1 of the above table, Futami et al. does not teach the XAA analog of the present invention, 5,6-dimethyl XAA (DMXAA), and therefore there can be no possibility whatsoever that the skilled artisan would arrive at the Examiner's conclusion in step 2 of the above table that Futami et al. teaches the use of DMXAA. Specifically, Futami et al. teaches the successful use of only the 5-substituted XAA analogs 5-methyl XAA and 5-chloro XAA; therefore, there is no disclosure or suggestion to use the 5- and 6-substituted XAA analog DMXAA, in complete contradiction to the Examiner's position as summarized in row 2 of the above table.

Equally to the point, Futami et al. show that a third XAA analog, 7-methyl XAA, has no ability to induce anticancer activity; given that a full 30% (1/3) analogs of XAA used by Futami et al. do not work, it is impossible to see how the Examiner is able to conclude that two operable examples and one inoperable example of XAA analogs would suggest the use of a completely different XAA analog, DMXAA.

Applicants note that the above conclusion is further strengthened by the Examiner's own explicit statement of the above observation, which was made in the section of the Office Action directed to enablement (Office Action of 1/16/07, page 3, bottom of block quote):

> In addition, not all [of] the analogue [sic] of XAA has [sic] a tumor restricted function, Futami et al., (J of Immunotherapy, vol 12, 247-255) indicates that 7-methyl-XAA; a analogue of XAA, self, or combination with IL-2 has not synergistic activity in suppression of tumor growth (page 252-253, col 1). Thus it would be undue experimentation to test

> two agents in combination in order to determine whether one skilled in the art could use them together for treating a large or advanced tumor.

Given that the Examiner is willing to make this undue experimentation argument in her enablement rejection, the Examiner must be equally willing to accept this argument with regard to her own obviousness rejection. Thus the Examiner must accept that this observation in Futami renders the Examiner's position regarding the extrapolation of Futami et al. to the DMXAA of the invention completely untenable.

Proceeding on to step 3 shown in the above table, although it is true that Olsson et al. show an increase in IL-2 levels as a result of administration of CAM B7.1, it is, with all due respect, something of a mischaracterization of Olsson et al.'s conclusion to say that this reference teaches that "Human IL-2 is induced by CD80 (B7.1) in cancer cells and T cells." See Office Action of 1/16/07, page 6 in top third of page. In fact, Olsson et al. is directed to understanding the effects of two different CAMs, CAM B7.1 (CD80) and CAM B7.2 (CD86), and the reference concludes that CAM B7.1 stimulates IL-2 production only as a stepping stone to the actual conclusion of the reference, i.e., that, unlike CAM B7.2., CAM B7.1 is needed to induce a wide variety of transcription factors, thereby inducing IL-2, which stimulates vigorous T-cell proliferation.

Equally as relevant, although it is true that the cell lines used in Olsson et al. are indeed cancer cell lines, nothing in Olsson et al. is directed to a discussion of the treatment of cancer, the use of B7.1 (or IL-2) in the treatment of cancer, etc. Applicants previously made this point in their showing in the Response of 11/2/06 that there is no motivation to combine Futami et al. and Olsson et al. because,

> Specifically, Futami discusses 1a) the treatment of cancer with a combination of FAA derivatives and 1b) the single exogenously administered purified cytokine IL-2, while Olsson 2a) does not teach or discuss any form of cancer whatsoever but instead teaches T cell activation 2b) not resulting in the single exogenously administered purified cytokine IL-2, but instead producing a multiplicity of

> heterogeneous effects including 2b1) T cell proliferation, 2b2) production of multiple cytokines (See Olsson, "Introduction,") and 2b3) production of multiple other proteins, e.g., multiple transcription factors including AP-1, NF-kB, CD28RE, and NF-AT (see Olsson, page 504, bottom of left column).

The above discussion is particularly relevant to step 4 of the Examiner's argument, in which she takes the statement that "Olsson et al., teach Human IL-2 is induced by CD80 (B7.1) in cancer cells and T cells" one step further and concludes that this observation indicates:

> that CD80 (B7.1)'s action on eradication of tumor is through induction of IL-2 and activation of T-cell by IL-2 for killing tumor cells. Therefore, replaced [sic] IL-2 with its stimulator B7.1 would result in same treatment effect and one of ordinary skill would be motivated to reached the claimed invention ...

Office Action of 1/16/07, page 6 in top third of page, emphasis added. Respectfully, this statement is based solely on the Examiner's own hindsight understanding of the invention; nowhere in the specification is the mode of action of any of the disclosed CAMs given, nor is there any indication whatsoever that these CAMs are mediated via IL-2 activity. Similarly, Olsson does not discuss cancer at all, and clearly does not discuss any involvement of IL-2 in cancer treatment, much less IL-2 mediation of CAM B7.1 action in cancer treatment. This statement is evidence of the Examiner's own desire to impose her own understanding of the mechanism of action in the present invention of the combination of CAMs and DMXAA (in one specific embodiment) to treat tumors which, while laudible, is impermissible hindsight.

Therefore on the basis of the above, it is clear that steps 3 and 4 of the Examiner's arguments are examples of impermissible conclusions obtained only through, at best, impermissible hindsight, and that these conclusions cannot serve as any basis for the Examiner's obviousness rejection.

In light of the above, it is clear that there is no logic available on which to obtain steps 5-6 of the Examiner's obviousness rejection, i.e., the Examiner's conclusion that the skilled artisan would, on the basis of Olsson et al. replace the IL-2 of Futami et al. with CAM B7.1, thereby obtaining the combination of CAM B7.1. and DMXAA.

In addition to the above arguments overcoming the Examiner's obviousness rejection, Applicants note there are additional reasons why the obviousness rejection must be withdrawn, and that, although these arguments were made in the previous Response of 11/22/06, the Examiner has not addressed these arguments.

Thus for example Applicants direct the Examiner's attention to the fact that Applicants showed previously that neither Futami et al. nor Olsson et al. teach a treatment for large or advanced tumor burdens, and that the Examiner has not addressed this fact in the most recent Office Action. Thus Applicants previously stated that the obviousness rejection did not provide every limitation of the claims, and specifically,

> In this regard, Applicants direct the Examiner's attention to the explicit limitation in all the claims that the methods of treatment of these claims must be successful for situations where there are "advanced or large" tumors or tumor burdens (see independent claims 1-4). As Applicants have stated previously neither Futami nor Olsson teach or remotely suggest the treatment of cancers with "advanced or large" tumors or tumor burdens. Therefore, the combination of these references similarly cannot teach this limitation, and, in light of this absence of teaching of this limitation, the prima facie case for obviousness has not been provided, and the rejection must be withdrawn.

Response of 11/22/06, middle of page 18. In the Office Action of 1/16/07, the Examiner stated that, with regard to this explicit limitation of the claims,

> In response to this argument, although the tumor size after 7 day inoculation of tumor cells is not explicitly described in the reference, one skilled in the art would know [that] injection of 10^5 tumor cells

> would result in formation of tumor colonies and certain size of the tumor 7 days after injection ... Moreover, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to optimize the treatment method according to the growth rate and condition of different tumors established in the mice comprising the tumor size and day or dose of the administration ...

With regard to this statement, respectfully, this is not germane to Applicants' argument, because the point is not whether the rate of growth of the tumor is known, the point is that neither Futami nor Olsson are directed to treating large or advanced tumors or tumor burdens, which is an explicit limitation of the claims. Perhaps more to the point, the "optimization" the Examiner refers to is another example of impermissible hindsight; neither Futami nor Olsson teach the treatment of large or advanced tumors or tumor burdens, and the "optimization" the Examiner refers to could occur only after one of ordinary skill in the art had seen the results of the present invention, not before. Therefore on this basis the Examiner is respectfully requested to specifically address the points raised by Applicants, or to withdraw the obviousness rejection.

Similarly, the Examiner is also respectfully requested to address another unanswered statement by Applicants, i.e., that the limitation of timing of delivery of the compounds of the present invention is not taught or suggested in the combination of Futami et al. and Olsson et al. Specifically, on page 19 of the Response of 11/22/06, Applicants stated that:

> In claims 12, 20, 28, 36, and 44, the tumor growth-restricting agent is administered after the administration of the CAM, and in claims 13, 21, 29, 37, and 45, the time of administration of growth-restricting agent is explicitly specified as being 12 to 48 hours after administration of the CAM. By contrast, Futami teaches the administration of tumor growth-restricting agent fully 168 hours (7 days) before administration of IL-2, i.e., 168 hours before administration of what the Examiner claims is the desired product of the administration of CAM (i.e., what is taught by Olsson). Although the Examiner states that, with regard to the timing of administration of compounds, "administering one reagent prior to another" would be prima facie obvious (See Office Action, page 8, end

> of second paragraph), based on the above it is impossible to see on what basis the Examiner is able to arrive at this conclusion.

Emphases in original. This argument has not been discussed by the Examiner at any point in the present Office Action. Perhaps the Examiner will continue to argue that, despite the remarks of Applicants, the shifting of the time course is prima facie obvious, as the Examiner had previously asserted (see block quote above). However, Applicants note that there was as specific reason why Applicants chose the timing of administration that they did, one that would not be prima facie obvious, but that rather depends upon the detailed understanding of the likely mechanism of action of the present invention. Thus as stated in ¶ 76 of the specification,

> Combined Therapy by Timed Delivery of B7.1 and DMXAA/FAA Eradicates Large Tumours. We hypothesized that simultaneous administration of the B7.1 pCDM8 expression vector and DMXAA/FAA might impair CAM-mediated anti-tumor immunity, as dying and necrotic tumor cells would not be able to adequately express B7.1. This notion proved correct, and hence established tumors (0.6-0.8 cm in diameter) were first treated with B7.1 to stimulate anti-tumor immunity, and DMXAA and FAA were administered one day later to retard tumor growth.

Obviously this argument is not available to the Examiner, as citing it would constitute impermissible hindsight. Notwithstanding, Applicants respectfully request that the Examiner either provide a response to the Applicants demonstration that the above limitation is not provided by the combination of Futami et al. and Olsson et al., or that the Examiner withdraw the obviousness rejection as it applies to the claims containing this limitation.

In summary, Applicants have shown above that, as they stated in the last Response of 11/22/06, the Examiner must withdraw the rejection of the claims as obvious in light of the combination of Futami et al. with Olsson et al., because there is no motivation to combine these references; there is no reasonable expectation of success when the references are combined; and, perhaps most significantly, and as

shown at length in the last Response and again above, even when combined, Futami et al. and Olsson et al. do not teach every limitation of the claims.

Although the above alone serves as adequate grounds for the withdrawal of the obviousness rejection, Applicants also note that they explicitly incorporate into this Response all of the arguments made in the previous Response of 11/22/06 with regards to the inapplicability of the obviousness rejection made by the Examiner. For example, Applicants previously discussed in detail how it would not be obvious to extrapolate from the use of a purified IL-2 as is provided in Futami et al. to IL-2 as obtained by administration of B7.1. See, e.g., page 17, first full paragraph of the Response of 11/22/06. This argument has not been addressed by the Examiner; Applicants incorporate it by reference into this Response, and request that it and all other unanswered arguments in the previous Response be answered by the Examiner, or that the obviousness rejection be withdrawn on this basis alone.

Conclusion

In light of the foregoing, Applicants submit that claims all of the pending claims, i.e., claims 1-4, 12-14, 20-22, 28-30, 36-38 and 44-46, are in condition for allowance and such allowance is respectfully requested. Should the Examiner feel that any unresolved issues remain in this case, the Examiner is encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

The Commissioner is hereby authorized to charge the $790.00 fee for the Request for Continued Examination (RCE), the $1,020.00 fee for the three-month extension of time and any other fee that may have been overlooked to Deposit Account No. 10-0223.

Respectfully submitted,

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